World Digestive Health Day
(WDHD)
Inflammatory Bowel Disease Epidemiology In the World and Iran

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Gastroenterologist
DDRI
96.2.28
• The prevalence of IBD:
  - continues to increase steadily in Western countries
  - and newly industrialized countries have a rapidly increasing incidence

• The global spread of IBD appears to associate with:
  - Westernization of diets
  - environment, and affects on intestinal microbiome
  - and increases the risk of IBD in genetically susceptible
The global burden of IBD: from 2015 to 2025

- Over 1 million residents in the USA and 2.5 million in Europe are estimated to have IBD, with substantial costs for health care.

- The majority of patients are diagnosed early in life and the incidence continues to rise.

- Therefore, the effect of IBD on health care systems will rise.

- IBD has emerged in newly industrialized countries in Asia, South America and Middle East.

- Understanding the worldwide epidemiological patterns of IBD will prepare us to manage the burden of IBD over time.
History
UC began in Western Europe in the 1800s, with the first case report published by Wilks and Moxon in 1859
• UC in Western Europe paralleled the advent of the industrial revolution in the 1800s

• A time when approximately 1 billion people lived on earth

• The industrial revolution led to:
  - increased urbanization
  - shift in economies from rural (agricultural) to urban

• The increasing population density within cities greatly changed diet and lifestyles today; these societal changes are called Westernization

• The incidence of UC slowly increased in the early 1900s in Western countries

Gastroenterology 2017;152:313–321
Regional ileitis in 1932 after the publication of a series of cases by Crohn (1884-1983)
• The 1950s was considered to be the start of the great acceleration of human civilization

• The incidence of UC and CD exploded in wealthy Westernized countries during the last 50 years of the 20th century

Gastroenterology 2017;152:313–321
History in Iran

- **Ghavami and Saidi.** Dis Colon Rectum 1969; 12: 462-466


The authors could only find UC and they both confirmed that they couldn’t find even a single case of CD


• Aghazedeh et al., J Gastroenterol Hepatol 2005; 20: 1691-5
Epidemiologic Characteristics of 500 Patients with Inflammatory Bowel Disease in Iran Studied from 2004 through 2007


Background: Despite claims of rarity, some studies indicate that the prevalence of inflammatory bowel disease has increased in Iran during the past decades. Establishment of a registry and the clinical characteristics are presented in this study.

Methods: Two hundred ninety-three patients with ulcerative colitis and 207 with Crohn’s disease, referred to tertiary referral gastrointestinal centers in Tehran from 2004 through 2007, were assessed. Demographic and clinical features, intestinal and extraintestinal manifestations, inflammatory bowel disease in relatives, measles infection and vaccination, nutrition during infancy, and drugs and surgical interventions were assessed.

Results: The mean±SD age at the diagnosis was 33.8±12.9 years in Crohn’s disease and 37.1±13.7 years in ulcerative colitis. Male:female ratio was 0.9:1.0 for Crohn’s disease and 0.7:1.0 for ulcerative colitis. A total of 177 (85.5%) patients with Crohn’s disease, and 254 (86.7%) patients with ulcerative colitis had never smoked. Measles vaccination was mentioned in 150 (72.5%) of Crohn’s disease and 214 (73%) of ulcerative colitis patients. Breastfeeding during infancy was reported in 178 (86%) and 257 (87.7%) of Crohn’s disease and ulcerative colitis patients, respectively. Appendectomy was reported in 37 (17.9%) of Crohn’s disease and 16 (5.5%) of ulcerative colitis patients, whereas tonsillectomy was reported in 11.6% of each group.

Conclusion: Demographic and clinical characteristics of inflammatory bowel disease patients are similar to that of other developing countries, in this study, more inflammatory bowel disease cases have been assessed in comparison with previous studies, which may be due to different time scales of socioeconomic evolution and environmental factors in Iran.
## Results

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Num. of patients (%)</td>
<td>293 (58.6)</td>
<td>207 (41.4)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>33.8 (12.9)</td>
<td>37.2 (13.7)</td>
</tr>
<tr>
<td>M/F</td>
<td>0.7/1</td>
<td>0.9/1</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>22.6 (3.9)</td>
<td>23.7 (4.2)</td>
</tr>
<tr>
<td>Family history (first degree)</td>
<td>18 (8.7)</td>
<td>28 (9.6)</td>
</tr>
<tr>
<td>Infantile Feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>257 (87.7)</td>
<td>178 (86)</td>
</tr>
<tr>
<td>Formula</td>
<td>28 (9.6)</td>
<td>25 (12.1)</td>
</tr>
<tr>
<td>Cow</td>
<td>8 (2.7)</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Measles infection</td>
<td>123 (42)</td>
<td>74 (35.7)</td>
</tr>
<tr>
<td>Measles vaccination</td>
<td>150 (72.5)</td>
<td>214 (73)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>39 (13.3)</td>
<td>30 (14.4)</td>
</tr>
</tbody>
</table>
Emerging Epidemic of Inflammatory Bowel Disease in a Middle Income Country: A Nation-wide Study from Iran


Abstract

Background: The burden of inflammatory bowel disease (IBD) hasn't been reported in Iran. We aimed to estimate the prevalence and incidence of IBD and its trend in Iran at national and subnational level from 1990 to 2012.

Methods: We conducted a systematic review of English and Persian databases about the epidemiology of IBD. We also collected outpatient data from 17 provinces of Iran using almost all public and private referral gastroenterology clinics. Prevalence and incidence rate was calculated at national and subnational levels. The Kriging method was used to extrapolate provinces with missing data and GPR model to calculate time trends of rates at subnational level.

Results: We found 16 case series, two population-based studies, and two review articles. We collected 11,000 IBD cases from outpatient databases. Among them, 9,269 (84.26%) had ulcerative colitis (UC), 1,846 (14.98%) had Crohn's disease (CD), and 85 had intermediate colitis (IC). A total of 5,452 (49.56%) patients were male. Mean age at diagnosis was 32.80 years (CI: 13 – 61) for UC and 29.98 years (CI: 11 – 58) for CD. Annual incidences of IBD, UC, and CD in 2012 were 3.11, 2.70, and 0.41 per 100,000 subjects respectively. Prevalence of IBD, UC, and CD in 2012 were 40.67, 35.52, and 5.03 per 100,000 subjects respectively. The incidence of UC and CD showed a significant increase during the study period (P for trend < 0.05).

Conclusions: The incidence and prevalence of IBD are increasing in Iran. Establishing a national IBD registry seems necessary for comprehensive care of IBD patients in Iran.
Many factors contributed to the increase in the incidence of IBD, including:

- increased awareness
- improved access to medical technology and health care providers
- development of surveillance systems
- and environmental exposures associated with Westernization of society
1st case of UC reported by Sir Walter Wilks

1st case of UC reported in China

Western World

Newly Industrialized Countries

1859

Industrial Revolution-1800s

1956

Great Acceleration of Populations-1950s

Globalization-21st Century
• The end of the 20th century is recognized as the onset of globalization:
  - industrializing countries in Asia, the Middle East
  - and South America became more Westernized

• Newly industrialized countries experienced:
  - rapid population growth, urbanization, industrialization
  - and Westernization of culture

• Systematic analyses confirmed that the incidence of UC, followed by that of CD, was increasing:
  - in Asia at the turn of the 21st century
  - similar to that observed in Western countries during the 20th century
• In 2017, IBD is a global disease with the highest prevalence in Western countries

• The peak in the incidence of IBD in newly industrialized countries is unknown

• India and China each exceeding 1 billion, the future global impact of IBD simply cannot be ignored
• In the United States, approximately 1.6 million Americans currently have IBD

• As many as 70,000 new cases of IBD are diagnosed each year

• The rise of IBD in newly industrialized countries parallels its growth in the Western world 30 to 40 years ago

• Gastroenterology 2017;152:313–321
• Since 2000, the prevalence of IBD has ranged from 0.3% to 0.5% in North America

• Similar high prevalence values have been reported:
  - Northern Europe (eg, United Kingdom and Scandinavia)
  - Western Europe (eg, Spain and Germany)
  - and Oceania (eg, New Zealand)

• The increase in the prevalence of IBD coincided with the great acceleration of the human population in the last half of the 20th century

Gastroenterology 2017;152:313–321
• The start of the 21st century, the incidence of IBD has been changing in Western countries

• Some population based studies have shown stabilization

• Some have reported a decreasing incidence of IBD

• Pediatric onset IBD continues to increase steadily in incidence

Gastroenterology 2017;152:313–321
• IBD is a chronic disease:
  - relatively low mortality
  - and diagnosed primarily in young age

• The prevalence of IBD increases over time such:
  - new diagnoses add to the base population
  - rate significantly higher than the loss of patients from a clinical practice

• The net effect is a steady increase in the prevalence of IBD over time
For example in Olmsted County, Minnesota, the prevalence of CD was:

- only 28 cases per 100,000 in 1965
- increasing to 90.5 per 100,000 in 1980
- increasing 132.7 per 100,000 in 1991
- increasing 213.9 per 100,000 in 2001
- and increasing 246.7 per 100,000 in 2011
• The increase in the prevalence of IBD in Western countries

• For example:
  - the prevalence of IBD in the USA was estimated to be slightly more than 0.5% in 2015
  - and increase to more than 0.6% in a decade
  - and approximately 2.2 million Americans living with IBD in 2025
• In contrast, newly industrialized countries in Asia, the Middle East, Africa, and South America have a low prevalence of IBD

• The prevalence of IBD:
  - in Japan was 76 cases per 100,000 in 2005
  - in South Korea was 42 per 100,000 in 2005
  - in Hong Kong was 43 per 100,000 in 2014
  - in Iran was 40.67 per 100,000 in 2012

  (AIM, Volume 19, Number 1, January 2016)
• The incidence of IBD in Asia is 1.4 cases per 100,000

• The highest incidence of IBD among the Asia Pacific Crohn’s and Colitis Epidemiologic Study countries is in India at 9.3 per 100,000 person years

• The incidence of IBD in China is 3.3 per 100,000

• The incidence of IBD in Iran; 3.11 (per 100000 in 2012)  
  (AIM, Volume 19, Number 1, January 2016)

• In Asia, UC is 2 fold more likely to be diagnosed than CD, although this ratio has been decreasing over time
• The incidence of IBD also is increasing rapidly in newly industrialized countries outside of Asia.

• For example, the incidence of CD and UC substantially increased in Piaui, Brazil, from 1988 to 2012.

• In Sao Paulo, Brazil, the incidence of IBD doubled from 4.5 per 100,000 (1991–1995) to 9.7 per 100,000 (2001–2005).

• Data from Uruguay and Barbados have shown patterns similar to those of Brazil.

• The incidence of IBD is increasing in Central and South America.
• The increase of IBD in newly industrialized countries parallels those of Western countries 30–40 years ago

• The increasing incidence of IBD:
  -in Europe and the USA since the 1950s
  -in Asia in the early 1990s (IRAN)
Data from 17 provinces and 36 referral centers

12635 IBD cases

Missing and out of date data=1563

Duplicates=255

11000 IBD cases

Patients from province without local data=1115

9885 IBD cases remained
The colleagues helped us:

1. Reza Malekzadeh
2. Parinaz Mehdipour
3. Nasser Ebrahimi Daryani
4. Mohammad Reza Zali
5. Fariborz Mansour Ghanaei
6. Alireza Safaripour
7. Rahim Aghazadeh
8. Hassan Vosoughinia
9. Hafez Fakheri
10. Mohammad Hossein Somi
11. Iraj Maleki
12. Vahid Hoseini
13. Mohammad Reza Ghadir
14. Hamed Daghaghzadeh
15. Payman Adibi
16. Hamid Tavakoli
17. Alireza Taghavi
18. Mohammad Javad Zahedi
19. Taghi Amiriani
20. Masoud Tabib
21. Zainab Alipour
22. Hossein Nobakht
23. Abbas Yazdanbod
24. Masoud Sadreddini
25. Alireza Bakhshipour
26. Ahmad Khosravi
27. Pejman Khosravi
28. Siavosh Naserimoghadam
29. Shahin Mera
30. Rasoul Sotoudehmanesh
31. Farhad Barazandeh
32. Peyman Arab
33. Nadieh Baniasadi
34. Seyyed Javad Pournaghi
Figure 4. The trend of national incidence of UC and CD during study period.

Figure 6. Prevalence of UC and CD during study period at national level.
In Iran

• We found that:
  - incidence of:
    - IBD; 3.11 (per 100000 in 2012)
    - CD; 0.41 (per 100000 in 2012)
    - UC; 2.70 (per 100000 in 2012)
  - prevalence of:
    - IBD; 40.67 (per 100000)
    - CD; 5.03 (per 100000)
    - UC; 35.52 (per 100000)
Emerging Epidemic of Inflammatory Bowel Disease in a Middle Income Country: A Nation-wide Study from Iran

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Abstract

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Keywords: Crohn’s disease, Burden, inflammatory bowel disease, Iran, prevalence, ulcerative colitis

Genetic Clues to Pathogenesis

- The lifetime risk of IBD in first degree relatives is at least 2 fold higher in Ashkenazi Jews than in non-Jews.

- Twin studies; supported the heritable component of CD & UC.

- CD has:
  - 20%–50% concordance between monozygotic twins
  - 10% concordance in dizygotic twins

- UC has:
  - 15% concordance between monozygotic twins
  - 5% concordance in dizygotic twins
In 2001, identified in the NOD2 gene (also called CARD15) that increased risk for CD

NOD2 is expressed in Paneth cells, which:
- are located predominantly in the terminal ileum at the base of intestinal crypts
• Patients with IBD carrying NOD2 mutations have:
  -increased numbers of mucosa adherent bacteria
  -decreased the anti-inflammatory cytokine IL10

• Patients with IBD carrying NOD2 and ATG16L1, alterations in the structure of gut microbiota, including:
  -decreased levels of Faecalibacterium
  -increased levels of Escherichia

Gastroenterology 2014;146:1489–1499
Three Common CARD15 Mutations are not Responsible for the Pathogenesis of Crohn’s Disease in Iranians

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ABSTRACT

Background/Aims: Crohn’s disease frequency has increased in recent years in Iran. Genetic and environmental factors predispose people to this disease. Mutation in Caspase Recruitment Domain 15 (CARD15) gene is the most well known genetic predisposing factor to this disease. Frequency of three common CARD15 mutations has been studied in different ethnic groups. We aimed to study the frequency of these mutations in Iranian patients affected with Crohn’s Disease.
Methodology: One hundred fifteen proved cases of Crohn Disease and 115 age and sex matched normal controls were recruited in this study. Lf1007fs, R702W and G908R mutations were studied by Polymerase Chain Reaction-Restriction Fragment Length Polymorphisms (PCR-RFLP) followed by sequencing the positive cases.

Results: Lf1007fs and G908R mutations were not found in either patients or age-sex matched controls. Just in two patients, R702W mutation was proved by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) and sequencing. None of these patients had ileal or fibrostenotic type of disease while 14.7% of total patients had strictureing type of disease. No complication was seen in these two patients while 50.4% of patients had acquired complications during the course of disease.

Conclusion: The three mutations described are not responsible for the pathogenesis of Crohn’s Disease in Iranians. The results are in accordance with other Asian nations’ studies on IBD Patients.

INTRODUCTION

proposed that gene-environment interactions play

HEPATO-GASTROENTEROLOGY 2010; 57:285-289
• In GWASs have identified more variants associated with IBD

• There are now more than 200 IBD risk loci

• Approximately 70% of IBD risk loci are shared with other immune mediated disorders such as:
  - type 1 DM, celiac disease, RA, AS
  - and psoriasis

*Gastroenterology 2017;152:313–321*
• Genetic risk for IBD varies among different populations:
  - African American
  - and Asian have a lower familial risk

• A meta analysis of genetic studies of different ethnic groups found most IBD risk loci to be shared among diverse ancestry groups (eg, African Americans, Caucasians, and Asians)

• There were only a few population specific risk loci, with heterogeneity in effect size or risk-allele frequency (such as in NOD2)

• This was reported in ethnic association study of CD and UC, comprising 86,640 Europeans and 9846 individuals of East Asian, Iranian, and Indian, which identified 38 new risk loci

Nat Genet 2015;47:979–986
Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations


Ulcerative colitis and Crohn's disease are the two main forms of inflammatory bowel disease (IBD). Here we report the first trans-ancestry association study of IBD, with genome-wide or Immunochip genotype data from an extended cohort of 86,640 European individuals and Immunochip data from 9,846 individuals of East Asian, Indian or Iranian descent. We implicate 38 loci in IBD risk for the first time. For the majority of the IBD risk loci, the direction and magnitude of effect are consistent in European and non-European cohorts. Nevertheless, we observe genetic heterogeneity between divergent populations at several established risk loci driven by differences in allele frequency (NOD2) or effect size (TNFSF15 and ATG16L1) or a combination of these factors (IL23R and IRGM). Our results provide biological insights into the pathogenesis of IBD and demonstrate the usefulness of trans-ancestry association studies for mapping loci associated with complex diseases and understanding genetic architecture across diverse populations.

IBD is composed of chronic, relapsing intestinal inflammatory diseases affecting more than 2.5 million people in Europe, with increasing prevalence in Asia and developing countries1,2. IBD is thought to arise from inappropriate activation of the intestinal mucosal immune system in response to commensal bacteria in a genetically susceptible host.

Thus far, 163 genetic loci have been associated with IBD via large-scale genome-wide association studies (GWAS)4,5. Outside of the human leukocyte antigen (HLA) region, the strongest associations have been identified outside the HLA region, the strongest associations have been identified outside of the human leukocyte antigen (HLA) region. Three of these loci (13q12, FCGR2A and SLC26A3) subsequently achieved genomewide significant evidence of association in European cohorts. The remaining three loci demonstrated a consistent direction of effect and nominally significant evidence of association (P < 1 x 10^-4) in previous European GWAS analyses4,5. A number of loci initially asso-
• Genetic studies have greatly increased our understanding of the pathogenesis of IBD

• It is still not clear:
  - why most individuals who carry IBD associated risk variants remain healthy
  - while others develop IBD
  - or even develop more than 1 immune mediated disease

• Increasing our understanding of:
  - interactions among genetic, environmental and microbial factors are specific risk factors, develop IBD
Environmental Determinants

- Environmental risk factors for IBD, including:
  - cigarette smoking (protects against UC in all regions; increases risk for CD in Western, but not in Eastern Asian, countries)
  - antibiotic use during childhood (increases risk in Western countries but reduces risk in Eastern Asian countries and Middle East)
  - breastfeeding (protects against IBD in a dose-dependent)
  - oral contraceptives (increases risk for CD)
  - appendectomy (protects against UC)
  - low levels of vitamin D (increases risk for CD)
  - and consumption of tea or coffee (reduces risk for CD and UC among Asians)

Gastroenterology 2017;152:313–321
The Hygiene Hypothesis

• Lack of stimulation of the immune system by environmental microorganisms and antigens in childhood may predispose to IBD

• Commensal gut organisms can stimulate regulatory T cells and prevent IBD in a mouse model

• Changes in intestinal microflora due to antibiotics use is associated with the onset of CD
The hygiene hypothesis, proposed by Strachan in the 19th century:
- increasing incidence of autoimmune
- and allergic diseases in industrialized nations

Factors inversely associated with risk of CD and UC include:
- having pets in childhood
- living on a farm, having a larger family
- and drinking unpasteurized milk

The hygiene hypothesis, may not apply to all populations worldwide

For instance, in India, measures of low hygiene were associated with an increased risk of UC

Sikh, Hindu, and Muslim migrants in the UK have a higher risk of UC than non migrants
Cold Chain hypothesis
-The cold chain hypothesis shows temporal and geographical coincidences between the development of the refrigerator and the outbreak of Crohn’s disease

-The potential link between the refrigeration of food and Crohn’s disease is via exposure to psychrotrophic bacteria with pathogenic properties such as:

= *Listeria monocytogenes*
= *Yersinia enterocolitica*
= *Clostridium botulinum*
= and *Bacillus cereus* which are surviving or developing at low temperatures
Crohn's Disease and Early Exposure to Domestic Refrigeration

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Abstract

Background: Environmental risk factors playing a causative role in Crohn's Disease (CD) remain largely unknown. Recently, it has been suggested that refrigerated food could be involved in disease development. We thus conducted a pilot case control study to explore the association of CD with the exposure to domestic refrigeration in childhood.

Methodology/Principal Findings: Using a standard questionnaire we interviewed 199 CD cases and 207 age-matched patients with irritable bowel syndrome (IBS) as controls. Cases and controls were followed by the same gastroenterologists of tertiary referral clinics in Tehran, Iran. The questionnaire focused on the date of the first acquisition of home refrigerator and freezer. Data were analysed by a multivariate logistic model. The current age was in average 34 years in CD cases and the percentage of females in the case and control groups were respectively 48.3% and 63.7%. Patients were exposed earlier than controls to the refrigerator ($X^2 = 9.9, df = 3, P = 0.04$) and refrigerator exposure at birth was found to be a risk factor for CD (OR = 2.08 (95% CI: 1.01–4.29), $P = 0.05$). Comparable results were obtained looking for the exposure to freezer at home. Finally, among the other recorded items reflecting the hygiene and comfort at home, we also found personal television, car and washing machine associated with CD.

Conclusion: This study supports the opinion that CD is associated with exposure to domestic refrigeration, among other household factors, during childhood.
Antibiotic use has been shown:
- to be a risk factor for IBD in Western countries
- and protective effect for IBD was reported for Asians and Middle Eastern migrants

Dig Dis Sci 2015; 60:290–298
Gut 2015;64:1063–1071

Maternal infections (and therefore antibiotic use) in the antepartum and peripartum periods do not affect the risk of development of IBD in offspring

Inflamm Bowel Dis 2017;23:635–640
Diet

• Transition of populations from rural regions to urban cities often is accompanied by:
  - greater food abundance, physical inactivity
  - and psychosocial stress

• Consumption of fat, refined sugar, and processed food has increased worldwide over the past 3 decades in developed and undeveloped countries

• Dietary fiber reduces risk, whereas dietary fat, animal protein, and sugar increase risk
• A study in Sweden associated consumption of fast food with an increased incidence of UC

• Northern France has a diet rich in beer, butter, eggs, and potatoes, increase risk of IBD

• Southern France has a Mediterranean diet, which includes many vegetables, fruits, fish, olive oil, and wine, and has been associated with a reduced risk of IBD
• Studies in animal models have shown that food additives, such as saccharin and sucralose, can increase the risk of diabetes, UC, and obesity

• In predisposed mice, carboxymethyl cellulose and polysorbate, common emulsifiers in most food, induced low grade gut inflammation and colitis

• Emulsifiers found in human foods; change the:
  - microbiota composition
  - and destroy the mucus layer, allowing microbiota to encroach on the epithelium
The Microbiome and Epidemiology

- 100 Trillion Microbes - 10 times more than cells in our body
- Estimated 500 species, 99% =30-40 species
- Resides in the Large Intestine where

70% of Body’s Immune System
Balance of gut microbiota can have a very real impact on immune system
• The intestinal microbiome has an important role in IBD pathogenesis

• Patients with IBD have broad changes in their intestinal microbiota profile compared with individuals without IBD

• The commensal gut microbiota is ecologically and functionally perturbed in patients with IBD
Newborn
- Initial gut bacteria (founder species) depends upon delivery mode
  - Vaginal delivery: *Lactobacillus, Prevotella* spp.
  - C-section: *Staphylococcus, Corynebacterium, Propionibacterium* spp.
  - Vertical inheritance from mother
  - Higher susceptibility to certain pathogens
  - Higher risk of atopic diseases

Early childhood
- New strains (less certain in origin) outcompete old ones
- Rapid increase in diversity
- Early microbiota development = high instability
- Shifts in response to diet, illness

Adult
- Highly distinct, differentiated microbiota
- Microbial community may continue to change, but at a slower rate than in childhood

Elderly
- Substantially different gut communities than in younger adults
Table 1 A modern lifestyle might be linked with alterations of gut microbial colonization

<table>
<thead>
<tr>
<th>Modern lifestyle</th>
<th>Traditional lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth in a hospital; increasing rate of caesarean delivery</td>
<td>Vaginal delivery at home</td>
</tr>
<tr>
<td>Small family size</td>
<td>Large family size, crowding</td>
</tr>
<tr>
<td>Often live in an urban setting, surrounded by concrete</td>
<td>Tend to live in a rural setting in contact with soil microorganisms</td>
</tr>
<tr>
<td>Sanitation of living spaces; environment colonized by resistant microorganisms</td>
<td>Ancestral colonization of the living environment</td>
</tr>
<tr>
<td>(including resistant bacteria, fungi and acari)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic usage early in life</td>
<td>No antibiotics in infant life</td>
</tr>
<tr>
<td>Daily body wash with hot water and soap</td>
<td>Limited access to hot water and soap</td>
</tr>
<tr>
<td>Low rate of <em>Helicobacter pylori</em> colonization</td>
<td>High rate of <em>Helicobacter pylori</em> colonization</td>
</tr>
<tr>
<td>Decline in endemic parasitism</td>
<td>Parasitic worms common</td>
</tr>
<tr>
<td>Food conserved by refrigeration</td>
<td>Food conserved by microbial fermentation</td>
</tr>
<tr>
<td>Consumption of processed foods</td>
<td>Consumption of natural foods</td>
</tr>
</tbody>
</table>

Manichanh, C. et al. (2012) *The gut microbiota in IBD*  
• Metagenomic studies; limited data from Asia, have reported:
  - reductions of Firmicutes, such as F prausnitzii
  - and increases in Escherichia coli, Fusobacterium, and Proteus, in patients with IBD

• One third of patients with CD have increased numbers of mucosa-associated, adherent-invasive E coli in ileal tissues

• The lower prevalence of helminths in industrialized societies have been proposed to increase the risk of IBD

• Small studies of the whipworm Trichuris suis ova in patients with CD produced meaningful changes in symptoms
Changes in the microbial profile:
- Roseburia hominis
- Clades IV
- XIVa Clostridia
- Faecalibacterium
- Prunusis
- Firmicutes
- Bifidobacterium
- Enterobacteriaceae
- Escherichia coli
- Fusobacterium
- adherent-invasive
- E coli (AIEC)
- Proteus

Healthy

IBD

<table>
<thead>
<tr>
<th>Smoking</th>
<th>CD: Risk in Caucasians and Middle Eastern migrants</th>
<th>UC: Protective in Caucasians and Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use in childhood</td>
<td>CD: Risk in Caucasians, protective in Asians/Middle Eastern migrants</td>
<td>UC: Risk in Caucasians, protective in Asians/Middle Eastern migrants</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>Protective in Asians and most studies in Caucasians</td>
<td>Protective in Asians and most studies in Caucasians</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>CD: Risk in Caucasians</td>
<td>UC: Inconclusive</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>CD: Risk in Caucasians</td>
<td>UC: Protective in Caucasians</td>
</tr>
<tr>
<td>Low levels of vitamin D</td>
<td>CD: Risk in Caucasians</td>
<td>UC: Risk in Caucasians</td>
</tr>
<tr>
<td>Tea or coffee consumption</td>
<td>CD: Protective in Asians</td>
<td>UC: Protective in Asians</td>
</tr>
</tbody>
</table>

Hygiene hypothesis:
- Having pets in childhood, living on a farm, larger family size, and drinking unpasteurized milk were inversely associated with the risk of CD and UC.

Changing diet:
- Introduction of packaged food, fast food chains, increased use of antibiotics, increased fat (monounsaturated and polyunsaturated fatty acids) consumption and sugar intake; less dietary fibers is associated with risk of IBD.

Dietary chemicals:
- Food additives – saccharin, sucralfate, carboxymethylcellulose and polysorbate-80, common emulsifiers (including polysorbates, sorbitol esters, lecithin), might increase risk of IBD (data are derived from animal models).

Over 200 IBD risk loci (37 specific for Crohn's disease and 32 for ulcerative colitis) have been discovered. However, modest fraction of predicted heritability can be explained by known genes or loci.
Preventing the Global Increase

• To stop the global increase of the incidence of IBD, we should direct our attention to factors associated with protection

• Potentially relevant environmental influences the spectrum from:
  - mode of birth, to early life exposures, to risk factors in adulthood
• Several environmental factors can be targeted to reduce the incidence of IBD

• First, cigarette smoking increases the risk of CD whereas quitting smoking increases the risk of UC

• Preventing smoking among adolescents could have the largest impact in reducing the incidence of IBD
• The protective effect of breastfeeding in IBD, as well as other autoimmune and allergic disorders, also has been established.

• Vitamin D supplementation may be a simple mechanism to reduce IBD incidence.

• Northern countries where there is widespread vitamin D deficiency.

• Several groups are potentially the most useful to study:
  - pediatric populations
  - high risk groups (first-degree relatives and multiplex families)
Reducing Incidence by Half by 2032

- We are far from preventing IBD or even reducing its increase in incidence

- With advances in our knowledge of IBD pathogenesis:
  - genetics, and the effects of the microbiome
  - and environmental factors on risk

- The IBD community should prioritize to cut the global incidence of IBD in half by 2032 the 100th anniversary of the discovery of CD
IBD registry project

A national project Administrator: Digestive Disease Research Institute, Tehran university of medical sciences 2016-Present
Whole Patients Enrolled: 7760 pts (19 provinces) still running
Blood samples: 300

Estimated all IBD pts: 20,000 – 30,000 persons
UC or CD

• Crohn disease: 25%
• Ulcerative Colitis: 75%
## Education Level

<table>
<thead>
<tr>
<th>Education Level</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid</td>
<td>7758</td>
<td>100.0</td>
</tr>
<tr>
<td>Missing</td>
<td>2021</td>
<td>26.0</td>
</tr>
<tr>
<td>Elementary</td>
<td>510</td>
<td>6.6</td>
</tr>
<tr>
<td>Middle</td>
<td>623</td>
<td>8.0</td>
</tr>
<tr>
<td>Diploma</td>
<td>1707</td>
<td>22.0</td>
</tr>
<tr>
<td>associate degree</td>
<td>418</td>
<td>5.4</td>
</tr>
<tr>
<td>bachelor degree</td>
<td>1622</td>
<td>20.9</td>
</tr>
<tr>
<td>master of science</td>
<td>504</td>
<td>6.5</td>
</tr>
<tr>
<td>Ph.D.</td>
<td>144</td>
<td>1.9</td>
</tr>
<tr>
<td>illiterate</td>
<td>209</td>
<td>2.7</td>
</tr>
<tr>
<td>Total</td>
<td>7758</td>
<td>100.0</td>
</tr>
</tbody>
</table>
## Site Of Involvement

<table>
<thead>
<tr>
<th>Valid</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MISSING</strong></td>
<td>1123</td>
<td>15.9</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>240</td>
<td>3.4</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>5341</td>
<td>75.5</td>
</tr>
<tr>
<td>BOTH</td>
<td>307</td>
<td>4.3</td>
</tr>
<tr>
<td>OTHERS</td>
<td>53</td>
<td>.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7069</td>
<td>100.0</td>
</tr>
</tbody>
</table>
### Crohn’s disease Lesions Location

<table>
<thead>
<tr>
<th>Location</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>6184</td>
<td>87.5</td>
</tr>
<tr>
<td>colon</td>
<td>395</td>
<td>5.6</td>
</tr>
<tr>
<td>S-Bowel</td>
<td>222</td>
<td>3.1</td>
</tr>
<tr>
<td>both</td>
<td>246</td>
<td>3.5</td>
</tr>
<tr>
<td>Others</td>
<td>22</td>
<td>.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7069</strong></td>
<td><strong>100.0</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7070</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
### Ulcerative Colitis lesions location

<table>
<thead>
<tr>
<th>Valid</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>missing</td>
<td>3619</td>
<td>51.2</td>
</tr>
<tr>
<td>Proctitis</td>
<td>424</td>
<td>6.0</td>
</tr>
<tr>
<td>Left colon</td>
<td>1562</td>
<td>22.1</td>
</tr>
<tr>
<td>Sub colitis</td>
<td>245</td>
<td>3.5</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>1013</td>
<td>14.3</td>
</tr>
<tr>
<td>Other</td>
<td>206</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7069</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Main Presentations

Abdiss
Bloodydiarrhea
Diarrhea
rectalbleeding
mouinstool
Weightloss
bloodinstool
Arthralgia
Nausea
Vomiting
LowBackPain
Constipation
OralUlcer
Fissure
fever
abdten
Jaundice
fistula
AbdTenderness
Arthritis
Perirectaldisease
Abscess

0.1
Treatment By Salicylates
Treatment By Immunomodulators
We have so much missing data, WHY?

i. The questionnaires filled by self report of the patients

ii. The Questioners are not enough oriented

iii. The Questioners have not motive enough

iv. Time limitation

v. Not enough collaboration of our GI colleagues
Financial Burden of IBD

- Cost of Care
  - Healthcare costs higher in US than any other country
  - Higher for people <20 years of age
  - Less than one-third of costs due to hospitalization
  - Estimated medical expenses for insured people (costs for insurer)
    - ~$19,000 per year for Crohn’s
    - ~$15,000 per year for ulcerative colitis

Park & Bass, *IBD* 2011
روز جهانی بیماری های التهابی روده

19 MAY